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EXAMINER	
ASHEN, JON BENJAMIN	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,525	MARTH ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-12 and 29-39* is/are pending in the application.

4a) Of the above claim(s) *31-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-12,29,30 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

1. Claims 1, 6-12 and 29-39 are pending in this application. Applicant has cancelled claims 2-5 and 13-28 and added new claims 29-39 in the communication filed 6/13/2005. Claims 1, 6-12 29-30 and 37-39 are currently under examination. Applicant's response filed 6/13/05 has been fully considered. Rejections and/or objections not reiterated from the previous office action mailed 2/10/05 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

2. Newly presented claims 31-36 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Applicant's original claims were drawn to methods of modulating the levels of vWF or FVIII in an animal comprising administering an agent that causes an increase or decrease in ST3Gal-IV sialyltransferase enzyme activity in the animal. The only agent presented, that was required to be administered in the method as originally filed, was an antisense nucleic acid agent (claim 4, now cancelled). Newly presented claims 31-36 are now drawn to methods of modulating levels of vWF or FVIII in an animal comprising

ST3Gal-IV substrate (claim 31) or a structural analog of a ST3Gal-IV substrate (claim 32) (including donor and acceptor substrates as listed in claims 33-36). However, the newly presented method claims require administration of a ST3Gal-IV sialyltransferase inhibitor agents that are structurally and functionally distinct from the antisense nucleic acid agents originally presented and would have been properly found to have Lack of Unity with the originally presented antisense nucleic acid agent for the following reasons.

The newly presented methods that require ST3Gal-IV sialyltransferase inhibitors that are competitive inhibitors of ST3Gal-IV substrate (claim 31) or structural analogs of a ST3Gal-IV substrate (claim 32) (including donor and acceptor substrates as listed in claims 33-36) do not relate to a single general inventive concept with originally presented antisense nucleic acid agents or each other under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features. Each of the agents are not of similar nature because, while each may be argued to share a common property or activity that is inhibiting ST3Gal-IV enzyme activity, each does not contain a common structure that is present, i.e., a significant structure is shared by all that is required for that activity and all of the presented agents do not belong to an art recognized class of compounds in the art to which the invention pertains.

Since applicant has received an action on the merits for the originally presented invention which was a method that required the use of an antisense nucleic acid agent, this invention has been constructively elected by original presentation for prosecution on

the merits. Accordingly, claims 31-36 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 6/20/2005 was filed after the mailing date of the first action on the merits on 02/10/2005. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Double Patenting

4. Claims 1 and 8-12 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5 and 8-10 of U.S. Patent No. 6,376,475 in view of Tsuji 1996 (J. Biochem. Vol. 1, pp. 1-14) for the reasons set forth in the Action mailed 02/10/2005.

5. Claims 1 and 8-12 of the instant application remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 9-11 and 16-21 of copending Application No. 10/398,520 for the reasons of record set forth in the Action mailed 02/0/2005. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The scope of claims 1 and 8-12 of the instant application is broadly drawn such that it either fully encompasses, or overlaps in claimed subject

matter, with claims 1, 9-11 and 16-21 of copending Application No. 10/398,520. Copending Application No. 10/398,520 and the instant application are both drawn to a method of administering an ST3Gal-IV sialyltransferase inhibitor that reduces the amounts of a cell-surface sialylated oligosaccharide wherein the sialylated oligosaccharide comprises a terminal α2-3-linked sialic acid. Claims in both the instant and copending applications which require co-administration (either in conjunction with or prior to) with a drug for which blood clotting or inflammation is a potential side effect are obvious over each other because both conditions are a result of reducing the level of biosynthesis of alpha 2,3 sialic acid terminated oligosaccharides.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

6. Applicant's arguments filed 6/13/05 have been fully considered but they are not persuasive. Applicant has argued that the claim limitation, "wherein said animal is suffering from or is at risk of developing atherosclerosis or a blood clotting disorder", which was newly introduced in claim 1 in the amendment filed 06/13/05, obviates the outstanding rejections under the judicially created doctrine of obviousness-type double patenting (bottom of pg. 5). Applicant asserts that there has been no showing of how any of the claims cited above would "motive one of skill in the art atherosclerosis or a blood clotting disorder, as presently recited in claim 1." It appears that some text is missing in this response. However, in the event that Applicant is arguing that one of

skill in the art would not be motivated by any of the claims in the '475 patent or the '520 Applicaton, to practice a method of modulating levels of vWF or FVIII in an animal comprising administering a ST3Gal-IV sialyltransferase inhibitor, "wherein said animal is suffering from or is at risk of developing atherosclerosis or a blood clotting disorder", this argument is addressed herein. The introduction of an intended use as a claim limitation does not impart patentably distinctness to the claim since the method steps remain the same. The inclusion of this limitation does not obviate the outstanding rejections because all animals are at some level of risk of developing atherosclerosis or a blood clotting disorder and a method of inhibiting an immune response or inflammation, both of which function based on the activity of a ST3Gal-IV sialyltransferase inhibitor, will also be, inherently, a treatment of animals that are at risk of developing atherosclerosis or a blood clotting disorder.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1 and 6-12 remain rejected and claims 29-30 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1, 6-12, 29-30 and 37-39 are drawn to a method for modulating levels of vWF or FVIII in an animal by administering an inhibitor of ST3Gal-IV sialyltransferase enzyme activity to an animal suffering from or at risk of developing atherosclerosis or a blood clotting disorder (claim 1) wherein the method is performed in conjunction with administration of a drug for which blood clotting is a potential side effect (claim 6) wherein the agent is administered before or simultaneously with said drug (claim 7) wherein the method is performed as a prophylactic or therapeutic measure against atherosclerosis (claims 8 and 10 respectively) wherein the atherosclerosis is associated with coronary artery disease or peripheral vascular disease (claims 9 and 11 respectively) wherein platelet formation is not significantly affected by administration of the agent to the animal (claim 12) wherein the method further comprises monitoring the animal for levels of vWF or FVII (claim 29) and further adjusting the dose of the ST3Gal-IV sialyltransferase inhibitor to maintain vWF at a desired level wherein the drug for which blood clotting is a potential side effect is selected from the group listed in claim 37 or is the drug or birth control agent listed in claims 38 and 39 respectively.

The instant claims read broadly on an *in vivo* method of treatment that functions in any animal by administering any inhibitor of ST3Gal-IV sialyltransferase enzyme activity to any animal that is at risk of developing atherosclerosis or a blood clotting disorder. The specification provides no limiting definition what is encompassed by the inhibitor of ST3Gal-IV sialyltransferase enzyme activity as claimed and no guidance as

to what inhibitor of ST3Gal-IV sialyltransferase enzyme activity, that can be any inhibitor of ST3Gal-IV sialyltransferase enzyme activity, will function in the method, *in vivo*, as claimed. The specification discloses examples of a single mammal that appears to be related to their invention as claimed that are heterozygous and null knockout mice in which the ST3Gal-IV sialyltransferase gene has been disrupted. However, the specification does not disclose or indicate possession of a method of treating these animals by either example or guidance which would lead the skilled artisan to a method of administering an effective amount of any inhibitor of ST3Gal-IV sialyltransferase enzyme activity, that would function, commensurate with what is now claimed, to provide a treatment. Neither does the specification provide a limiting definition, examples or specific guidance that would lead the skilled artisan to treat "an animal that is at risk of developing atherosclerosis or a blood clotting disorder" such that possession of a method of treating an animal that is at risk of developing atherosclerosis or a blood clotting disorder was shown.

The specification provides only limited and general guidance in regards sialyltransferase inhibitors that are known in the art to function *in vitro* and indicates that ST3Gal-IV activity can be regulated by modulation of the phosphorylation state of the enzyme, also *in vitro* (pg. 13). The specification further discloses that, "Additional inhibitors of the ST3Gal-IV sialyltransferase can be readily identified by screening methods known to those of skill in the art" and that these methods are assays of enzyme activity that are carried out *in vitro* (pg. 14). The specification, however, provides no examples of inhibitor of ST3Gal-IV sialyltransferase enzyme activity that

function *in vivo*, to provide the method of treatment as claimed. Additionally, the specification provides no specific guidance that would lead one skilled in the art to the structure of any particular molecules that would function as inhibitor of ST3Gal-IV sialyltransferase enzyme activity in the method of treatment as claimed.

The specification provides no structure of an inhibitor of ST3Gal-IV sialyltransferase enzyme activity that can be any inhibitor of ST3Gal-IV sialyltransferase enzyme activity that is required to function commensurate with what is now claimed, that will provide an *in vivo* treatment by practicing the method as claimed. Additionally, the specification provides no evidence for any shared distinguishing identifying characteristics of an inhibitor of ST3Gal-IV sialyltransferase enzyme activity that would be a shared and defining characteristic for the genus as claimed. To provide evidence of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In the instant case, what is the structure of an inhibitor of ST3Gal-IV sialyltransferase enzyme activity that can be any inhibitor of ST3Gal-IV sialyltransferase enzyme activity that would function to cause a decrease in ST3Gal-IV enzyme activity in any animal, *in vivo*, such that a treatment (e.g., the levels of vWF or FVIII are decreased in the animal) was provided, for example?

Applicant, therefore, has claimed a method of achieving a biological effect but has disclosed no compounds that can accomplish that result. Applicant has only provided an invitation for further experimentation to determine what particular agents or antisense nucleic acids could be used in the method of treatment as claimed. Applicant has not provided an adequate written description that indicates that applicant was in possession of a method of treatment because said method of treatment relies on the function of an inhibitor of ST3Gal-IV sialyltransferase enzyme activity for which a structure that corresponds with said function is not adequately described.

MPEP § 2163[R-2] I. states:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., > Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003);< Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.
>
> The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc., 935 F.2d at 1563-64, 19 USPQ2d at 1117.
>
> Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").
>
> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. > Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613.<

In the instant case, Applicant has not provided adequate written description of their invention because the specification does not convey, with reasonable clarity to those of skill in the art, as of the filing date sought, that applicant was in possession of the invention now claimed. Applicant has not shown how the invention was "ready for patenting" such as by the disclosure of the structure of an inhibitor of ST3Gal-IV sialyltransferase activity, that is required by the instantly claimed method, that will function commensurate with the breadth of what is now claimed, that will provide an *in vivo* treatment or by the description of any distinguishing identifying characteristics of an inhibitor of ST3Gal-IV sialyltransferase enzyme activity sufficient to show that the applicant was in possession of the broad genus as claimed. The claimed method depends on finding an inhibitor of ST3Gal-IV sialyltransferase activity, that will function in the method of treatment as claimed. Without such an inhibitor of ST3Gal-IV sialyltransferase activity, it is impossible to practice the method as claimed. It means little to invent a method if one does not have possession of an agent or antisense nucleic acid that is essential to practicing that method.

Moreover, Applicant has not provided any guidance, examples or distinguishing identifying characteristics of the method that will treat any animal that is at risk of developing atherosclerosis or a blood clotting disorder. Applicant has not indicated how they were in possession of a method that treats any animal that is at risk from developing atherosclerosis or a blood clotting disorder, such as by an example or guidance in the specification and the skilled artisan cannot determine that Applicant was in possession of such broad genus of method because the skilled artisan cannot

envision how any animal is not at some level of risk of developing atherosclerosis or a blood clotting disorder.

Therefore, Applicants have not provided an adequate written description of their invention which indicates that they were in possession of what is now claimed.

Response to Arguments

9. Applicant's arguments filed 6/13/05 have been fully considered but they are not persuasive. Applicant has argued that their amendment of 6/13/05, which specifies, "an inhibitor of ST3Gal-IV sialyltransferase activity" in place of an "agent" in claim 1 is sufficient to overcome the rejection of the instant claims under 35 U.S.C. 112, first paragraph, written description because these inhibitors are well known in the art and routine methods of screening for inhibitors are disclosed in the specification (pg. 7, 1st paragraph). Applicant has argued that the underlying inquiry with regard to written description is not whether the "exact structure" of a species, nor how many species, of a particular recited element are described in the specification. Instead, the underlying inquiry in determining compliance with the written description requirement is whether the specification describes the claimed invention in sufficient detail that one of skill in the art can reasonably conclude that the inventor had possession of the claimed invention. This argument is correct in part in that the underlying inquiry is whether the specification describes the claimed invention in sufficient detail that one of skill in the art can reasonably conclude that the inventor had possession of the claimed invention. However, it is not persuasive in the context of what Applicant has claimed, which is not

a composition that is the inhibitor of ST3Gal-IV sialyltransferase enzyme activity itself, wherein such compounds may be known in the art from *in vitro* studies, but a method of treatment that requires the function of an inhibitor of ST3Gal-IV sialyltransferase enzyme activity *in vivo*, wherein the inhibitor of ST3Gal-IV sialyltransferase enzyme activity can be any inhibitor and the animal to be treated is any animal that is at risk of developing atherosclerosis or a blood clotting disorder. It is this method that Applicant has not shown possession of.

Applicant has argued that they have flexibility in how possession is shown and argues that this is the case particularly where a recited element is auxiliary to the claimed invention (pg. 8, 2nd paragraph). However, this argument is not persuasive because the recited elements referred to in the instant application are the inhibitors of ST3Gal-IV sialyltransferase enzyme activity that are required to practice the instantly claimed methods. It is not clear how Applicant can argue that these elements are auxiliary to the invention.

Applicant argues that because the instant invention is not the discovery of ST3Gal-IV sialyltransferase inhibitors, but their use in new methods, and because enzymatic inhibitors of sialyltransferases were known in the art, identification of the inhibitors by their function is entirely proper and that the recitation of function in this case would "lead one having ordinary skill in the art" to a class of compounds having this function (pg. 9, 1st full paragraph). However, this argument is not persuasive in the context of what Applicant has claimed, which is not a composition that is the inhibitor of ST3Gal-IV sialyltransferase enzyme activity itself, wherein such compounds may be

known in the art from *in vitro* studies, but a method of treatment that requires the function of an inhibitor of ST3Gal-IV sialyltransferase enzyme activity *in vivo*, wherein the inhibitor of ST3Gal-IV sialyltransferase enzyme activity can be any inhibitor and the animal to be treated is any animal that is at risk of developing atherosclerosis or a blood clotting disorder. It is this method that Applicant has not shown possession of.

Applicant has argued that there is no ban on functional language in a claim and that a rejection under 112 1st paragraph is improper where functional language is not used to describe a point of novelty and pointed to claims that included a recitation of "inorganic salt capable of " that appear in Fuetterer. Applicant has then argued that like the inorganic salts of Fuetterer, the sialyltransferase inhibitors recited in the method of claim 1 are defined by their ability to carry out a particular function (inhibiting a certain enzyme), not by their chemical structure. The particular structure of the inhibitor used is not critical to the invention so long as the desired function is achieved. The ruling in Fuetterer makes clear that inhibitors not specifically disclosed in the present application are properly within the scope of Applicants' contribution to the art. Thus, the claims should not be so restricted that they can be avoided simply my using an inhibitor different from those specifically exemplified in the application.

However, contrary to Applicant's assertion, the inorganic salts of Fuetterer are not like the sialyltransferase inhibitors required by the method of claim 1. Although they are defined by their ability to carry out a particular function, the inorganic salts of Fuetterer are a broad class of chemically related compounds which the art recognized as being any inorganic salt that had such properties that was usable in his combination.

The instant claims are drawn to methods that require the function of a broad class of inhibitors of ST3Gal-IV sialyltransferase enzyme activity *in vivo*, a function that is not art recognized for the broad class of inhibitors of ST3Gal-IV sialyltransferase activity, which are known and disclosed from *in vitro* assays. In this case, the particular structure of an inhibitor as claimed, wherein the desired function is a function *in vivo*, is required because the art does not recognize that the desired function would be achieved by any inhibitor, but would require, as set forth above, specific guidance as to what inhibitors will function in the method as claimed, to provide a treatment, *in vivo*. It is not clear what Applicants are arguing in contending that the claims should not be so restricted that they can be avoided simply by using an inhibitor different from those specifically exemplified in the application, because no examples of methods of treatment are provided by the disclosure.

10. Claims 1 and 6-12 remain rejected and claims 29-30 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case, the specification does not provide an adequate written description of the inhibitors of ST3Gal-IV sialyltransferase enzyme activity that are required to practice the method of the invention as claimed (see previous rejection herein). Therefore, because the skilled artisan cannot envision any particular inhibitors of ST3Gal-IV sialyltransferase enzyme

activity that will function in the method of treatment or prevention as claimed, the specification does not enable a person skilled in the art to which it pertains to make and use the invention as claimed.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claims 1, 6-12, 29-30 and 37-39 are drawn to a method for modulating levels of vWF or FVIII in an animal by administering an agent that causes a decrease in ST3Gal-IV sialyltransferase enzyme activity in the animal, the full breadth of which is described in a previous rejection herein. All claims read broadly on a method of treatment comprising administering any inhibitors of ST3Gal-IV sialyltransferase activity to an animal at risk of developing atherosclerosis or a blood clotting disorder. In particular, claims 8 and 9 are drawn to a prophylactic method.

The specification, however, does not support the broad scope of the claims which encompass a method for modulating any levels of vWF or FVIII in any animal or any animal at risk (as above) by administering any inhibitor of ST3Gal-IV sialyltransferase enzyme activity that will cause a decrease in the levels of vWF or FVIII in the animal or the animal at risk. Additionally, the specification as filed provides no

support for claims to a method of treatment comprising administering an inhibitor of ST3Gal-IV sialyltransferase enzyme activity that will act as a prophylactic of atherosclerosis, in any animal, wherein that inhibitor can be any inhibitor of ST3Gal-IV sialyltransferase enzyme activity that causes a decrease in the levels of vWF or FVIII. Prophylactic, as defined by Webster's II New Riverside University Dictionary, means, "Serving to defend against or prevent something, esp. disease: PROTECTIVE" (pg. 944; also see the definition of prevent, pg. 933). Applying the dictionary definition to prophylactic, a reasonable interpretation of the nature of the invention is a method of preventing atherosclerosis or a blood clotting disorder due to any cause by administering any inhibitors of ST3Gal-IV sialyltransferase enzyme activity that causes any decrease in the levels of vWF or FVIII in any animal. The specification does not establish a predictable scheme for treating or preventing atherosclerosis or a blood clotting disorder by reducing or increasing the activity of ST3Gal-IV in any animal using any inhibitor of ST3Gal-IV sialyltransferase enzyme activity with an expectation of obtaining the desired biological function. The specification provides no specific guidance and presents no specific disclosures that would allow the skilled artisan to envision what inhibitor of ST3Gal-IV sialyltransferase enzyme activity would be required to practice a method of prevention or treatment as claimed.

The disclosures of the specification provide information concerning the biological effects of disrupting ST3Gal-IV sialyltransferase enzyme activity in knockout heterozygous and null mice. This disclosure provides a starting point for a series of experiments that would be required to determine how to formulate a method of

prevention or treatment as claimed, including a full characterization of the functional regions of all other ST3Gal-IV gene sequences and the determination of the particular effects of modulating ST3Gal-IV gene expression or ST3Gal-IV sialyltransferase enzyme activity on the levels of vWF and/or FVIII in all other animals. Once determined, the information from the above experiments could be used in a further series of experiments to determine what particular agents or antisense nucleic acids would be required to provide a prevention or treatment as claimed. Therefore, applicant has only provided an invitation for further experimentation, since the specification is entirely prophetic in regards to a method of prevention or treatment as claimed, and provides no specific guidance for determining how the skilled artisan would practice the method of prevention or treatment of the instant invention.

Additionally, because the breadth of the claims is so broad and because no specific or functional species inhibitors of ST3Gal-IV sialyltransferase enzyme activity that would be necessary to practice the method of prevention or treatment as claimed are disclosed in the specification, the skilled artisan would have to perform an extremely large and undue quantity of *de novo* trial and error experimentation (as indicated above) in order to determine, *de novo,* the structure and function of an inhibitor of ST3Gal-IV sialyltransferase enzyme activity that would function to cause a decrease in vWF or FVIII levels in any animal or any animal at risk (as above), so as to provide an *in vivo* prevention or treatment as claimed.

The state of the prior art at the time of filing recognizes a broad genus of inhibitors of ST3Gal-IV sialyltransferase enzyme activity that are known from *in vitro*

assays. Such inhibitors can include small molecules, peptides, aptamers, antibodies, siRNAs, ribozymes and sense and antisense oligonucleotides, for example. However, sound scientific reasoning requires that although such inhibitors can have the effects set forth above, determination of a particular and desired biological effect that results from a method of treatment, *in vivo*, using a specific inhibitor, would require, at least, that inhibitor. Without the inhibitor such a determination cannot be made.

In particular, with regard to antisense nucleic acids (because the instant claims still read on antisense nucleic acids which, in light of the lack of limiting definition provided by Applicant in the specification, are reasonably interpreted to be comprised in the broad class of inhibitors of ST3Gal-IV sialyltransferase enzyme activity), the state of the art at the time of filing relative to the enablement of nucleic acid therapies *in vivo* is reviewed by Opalinska et al. 2002 (Nature Reviews, Vol. 1, pp. 503-514). These authors provide a review of the challenges that remain before nucleic acid therapy becomes routine in therapeutic settings and clearly indicate that the art of nucleic acid therapy remains highly unpredictable and unreliable, particularly *in vivo*. According to Opalinska et al., "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain. The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field" (pg 503). Opalinska et al. also note that .. "[I]t is widely appreciated that the ability of nucleic acid

molecules to modify gene expression *in vivo* is quite variable and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and "In mRNA, sequence accessibility is dictated by internal base pairing and the proteins that associate with the RNA in a living cell. Attempts to accurately predict the *in vivo* structure of RNA have been fraught with difficulty. Accordingly, mRNA targeting is largely a random process" (pg. 511). The instant specification does not show how one in the art might overcome the obstacles to providing antisense therapy as outlined above or how applicant has overcome the same general obstacles to antisense therapy in the instant invention.

This view is supported by Branch (1998) who teaches that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch also teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable wherein they recite, "Recent studies emphasize the extent to which native RNA structure restricts the binding of ODN's... [B]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their

ability to act inside cells. Monia and co-workers used northern hybridization to screen 34 20-nt long s-ODNs complementary to c-*raf* kinase and found only one that yielded a greater than fivefold reduction in the target mRNA. Thus only 3% of the antisense molecules tested in this system were highly effective, 40% had almost no effect." (pg. 49).

The state of the prior art at the time of filing recognizes that there is a high degree of unpredictability in the art of *in vivo* nucleic acid therapy. There is no way of predicting, *a priori*, the ability to provide an *in vivo* treatment that relies on the modulation of gene expression or the efficacy of a treatment that relies on modulating gene expression comprising administering an agent that is any antisense nucleic acid.

Therefore, based on the nature of the invention as an *in vivo* method of prevention or treatment, the degree of unpredictability in the art of antisense nucleic acid therapy (which reasonably reads on the instantly claimed methods of treatment), the breadth of the claimed method as an *in vivo* method of prevention or treatment, the lack of guidance as to what particular species of inhibitor of ST3Gal-IV sialyltransferase enzyme activity would be required to practice the method as claimed, the need to screen multiple species of said inhibitors so as to allow identification of particular species as functional within the method as claimed and the quantity of *de novo* experimentation necessary to discover the above, an undue amount of experimentation would be required in order to practice the method of prevention or treatment as claimed. Therefore, the inventors have not enabled one skilled in the art perform the method of the claimed invention.

Response to Arguments

11. Applicant's arguments filed 6/13/05 have been fully considered but they are not persuasive. Applicant has argued that the outstanding rejection under 112 1st paragraph, enablement, is obviated by the present amendment to the claims to recite an "enzymatic inhibitor of ST3Gal-IV sialyltransferase activity" (pg. 11, 1st paragraph). However, contrary to Applicants assertion, the claims as amended, do not recite, "enzymatic inhibitor of ST3Gal-IV sialyltransferase activity." The claims as amended recite, "an inhibitor of ST3Gal-IV sialyltransferase enzyme activity" which, as set forth above and reiterated here, is reasonably interpreted to read on antisense nucleic acids, because antisense nucleic acids would inhibit the expression of ST3Gal-IV sialyltransferase, thereby inhibiting the enzyme activity of ST3Gal-IV sialyltransferase.

Applicant has argued that to the extent that the Examiner relies on an alleged lack of written description for the claimed invention as supporting the enablement rejection, this aspect of the rejection is overcome in part and traversed in part in view of the amendments and reasons set forth above regarding compliance with the written description requirement (pg. 11, 2nd paragraph). This argument was fully considered and not found to be persuasive (see above, Response to Arguments, Section 9).

Applicant has argued that the experimentation required to enable the instantly claimed methods would not be undue because sialyltransferases were well characterized at the time of the invention and assays for measuring ST3Gal-IV activity were well known and described in the specification as being usable to evaluate the inhibitory activity of a compound and that nothing in the outstanding rejection shows that

the specification does not provide a reasonable amount of guidance with respect to the direction in which experimentation using such assays should proceed (pg. 11, 3rd paragraph bridge to pg. 12, 1st partial paragraph). However, contrary to Applicants assertions and arguments, the instant claims are not drawn to methods of assaying for inhibitors of ST3Gal-IV sialyltransferase enzyme activity and are not drawn to the inhibitors themselves, but to methods of *in vivo* treatment that require administration of inhibitors that will function to decrease the levels of vWF or FVIII in any animal *in vivo*. The guidance the specification provides in regards to assay methods for screening for inhibitors that are required to function *in vivo* is insufficient to provide the skilled artisan with direction in regards to the claimed *in vivo* methods and determination of what inhibitors of ST3Gal-IV sialyltransferase enzyme activity would be functional in the instant methods of *in vivo* treatment as claimed, would be undue in light of the complete lack of guidance disclosed in the specification in regards to any particular inhibitors, that are required by the instantly claimed methods, will actually function *in vivo*.

Applicant has argued that that they have shown an *in vivo* effect of ST3Gal-IV sialyltransferase inhibition (presumably they refer to their knockout mouse here) that is a reduction in vWF and FVIII levels. Applicant has argued that because vWF and FVIII are known risk factors for atherosclerosis and blood clotting disorders, the skilled artisan would reasonably accept that *in vivo* inhibition of ST3Gal-IV activity would ameliorate or reduce the risk of such conditions. These arguments are indeed correct, but do not particularly address the outstanding grounds of rejection. Applicant is correct in arguing that the skilled artisan would reasonably accept that the knockout model shows *in vivo*

reduction of the levels of vWF and FVIII, that vWF and FVIII were known risk factors for atherosclerosis and blood clotting disorders and that reduction in these levels might ameliorate or reduce the risk of such conditions. However, the claims are not drawn to a method of making a transgenic knockout mouse model but rather to a method of *in vivo* treatment. The skilled artisan would not reasonably accept that they could perform a method of treatment as claimed, that required the administration of an inhibitor of ST3Gal-IV sialyltransferase enzyme activity (which could be any inhibitor) to provide a decrease in vWF or FVIII in any animal, *in vivo*, without undue, *de novo*, trial and error experimentation.

Applicant has emphasized that the Examiner bears the initial burden of providing evidence or reasoning why the claims are not enabled and stated that the examiner has not provided any reasoning or evidence to establish non-enablement of prophylactic or therapeutic use of lowering vWF levels via administration of an enzymatic inhibitor of ST3Gal-IV sialyltransferase (pg. 12 bottom bridge to pg. 13, top). It is not clear what Applicant is arguing here because the claims are not drawn to enzymatic inhibitors of ST3Gal-IV sialyltransferase but to methods of *in vivo* treatment comprising administering inhibitors of ST3Gal-IV sialyltransferase enzyme activity and both evidence and reasoning have been provided, in both this and the prior Action mailed 2/10/2005, why the claims are not enabled (see above and pgs. 12-18, section 11 of the prior Action).

In summary, the establishment of an *in vivo* biological effect of ST3Gal-IV sialyltransferase enzyme inhibition using an animal model is indeed important scientific

information. However, although this information may establish a correlation between the activity of a particular enzyme in an organism and putative disease or disorder states, this information alone is insufficient to provide an enabling disclosure for a method of treatment. It is merely prophetic that such a method may be effective. Additionally, the knowledge in the art, of ST3Gal-IV sialyltransferase inhibitors, and of routine assays of determining additional compounds that will act as inhibitors of ST3Gal-IV sialyltransferase enzyme activity, *in vitro*, is not sufficient to enable the instantly claimed methods of treatment that require the administration of inhibitors of ST3Gal-IV sialyltransferase enzyme activity to an animal, to achieve a particular and claimed biological effect *in vivo*.

Claim Rejections - 35 USC § 102

12. Claims 1 and 8-12 remain rejected under 35 U.S.C. 102(e) as being anticipated by Kapitonov et al. (U.S. Patent 6,280,989) for the reasons set forth in the Action mailed 2/10/2005 and reiterated herein. The invention as set forth in claims 1 and 8-12 is relied upon as above.

Kapitonov et al. disclose the identification of three novel classes of sialyltransferases, one of which is ST3Gal-IV (col. 2, lines 27-31). Kapitonov et al. also disclose that their invention relates to "methods of regulating a biological response in which a sialyltransferase or a homolog or modification thereof, of the present invention, participates, e.g., by modifying a substrate such as a glycoprotein or glycolipid which is a participant which leads to the ultimate cellular response. These pathways can be

modulated by administering various agents including antibodies to sialyltransferases, polypeptide mimics of sialyltransferases (e.g., which compete for substrates of the enzyme, antisense oligonucleotides, antisense mRNA, etc" (col. 16, lines 80-19) and that antisense oligonucleotides of the invention can be designed to specific regions of a sialyltransferase RNA and can then be administered to cells expressing such genes so as to inhibit expression (col. 18, lines 26-40) and that administering can mean contacting a cell or host in an effective manner with an agent of interest whereby the agent can modulate the activity of interest (col. 19, lines 65-67 bridge to col. 20, lines 1-2). It is noted herein, that claim limitations which require a reduction of ST3Gal-IV sialyltransferase enzyme activity are met by an antisense nucleic acid that will inhibit the expression of ST3Gal-IV sialyltransferase in that it reduces the overall levels of ST3Gal-IV sialyltransferase enzyme. The disclosure of Kapitonov et al. is considered to be enabling for the methods disclosed to at least the same extent as the disclosure of the instant application is enabling for the instantly claimed methods

In particular regards to claims 8-12, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In the instant case, a method of administering an inhibitor of ST3Gal-IV sialyltransferase enzyme activity

which causes a decrease in the activity of any sialyltransferase involved in ST3Gal-IV activity in an animal would also be a method that is performed as a prophylactic or therapeutic against atherosclerosis or wherein platelet formation is not significantly affected by administration. This is particularly evident when considering that the disclosure of the specification does not set forth any method steps by which the method of administration now claimed is to be performed. Therefore, the prior art is applied on the basis of the prior art disclosure of the claimed composition. MPEP § 2111.02.

Therefore, Kapitonov et al. anticipate each and every aspect of the invention as set forth in claims 1 and 8-12.

Response to Arguments

13. Applicant's arguments filed 6/13/05 have been fully considered but they are not persuasive. Applicant has argued that the outstanding rejection is overcome by amendment of claim 1 because Kapitonov does not disclose each and every limitation of the amended claim 1. Applicant argues that in particular, Kapitonov does not disclose administering a ST3Gal-IV sialyltransferase inhibitor to an animal suffering from or at risk of developing atherosclerosis or a blood clotting disorder. However, this argument is not persuasive because Kapitonov does disclose administering a ST3Gal-IV sialyltransferase inhibitor to an animal suffering from or at risk of developing atherosclerosis or a blood clotting disorder because all animals are inherently at some level of risk of developing atherosclerosis or a blood clotting disorder

Claim Rejections - 35 USC § 103

14. Claims 1 and 8-12 remain rejected under 35 U.S.C. 103(a) as being obvious over Marth et al. (U.S. Patent No. 6,376,475) in view of Tsuji 1996 (J. Biochem. Vol. 1, pp. 1-14) for the reasons of record as set forth in the Action mailed 02/10/2005.

Response to Arguments

15. Applicant's arguments filed 6/13/2005 have been fully considered but they are not persuasive. Applicant has argued that the outstanding rejection is overcome by amendment of claim 1 because there has been no showing of how one of ordinary skill in the art would be motivated to combine Marth et al. (U.S. Patent No. 6,376,475) in view of Tsuji 1996 to administer a sialyltransferase inhibitor to an animal suffering from or at risk of developing atherosclerosis or a blood clotting disorder. However, this argument is not persuasive because the motivation to combine the prior art references is sufficiently set forth in the prior Action and all animals are inherently at some level of risk of developing atherosclerosis or a blood clotting disorder.

Conclusion

16. No claims are allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jba

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